UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,221	08/22/2001	Florence Marciacq	025219-342	1827

7590 08/11/2003

Burns Doane Swecker & Mathis
George Mason Building
Washington & Prince Streets
PO Box 1404
Alexandria, VA 22313-1404

EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	12

DATE MAILED: 08/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,221	MARCIACQ ET AL.	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *12-15* is/are allowed.

6)☒ Claim(s) *1-11,16 and 18-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's Response dated May 22, 2003

1. In the Response filed May 22, 2003, claim 17 was canceled; claims 1-16, 18-27, and 30-33 were amended; no new claims were added. Applicant presented arguments directed to the rejection of claims 1-33 under 35 U.S.C. 112, first paragraph. A Declaration of Didier Molko, D.Sc., Ph.D. was submitted in support of applicant's position. Applicant also presented arguments to the rejection of claim 3 under 35 U.S.C. 112, second paragraph, and the rejection of claims 1-16 under 35 U.S.C. 103(a). An Information Disclosure Statement was also presented for consideration. Claims 1-16 and 18-33 are pending. An action on the merits of claims 1-16 and 18-33 is contained herein below.

2. The rejection of claims 16-17 under 35 U.S.C. 101 has been rendered moot by Applicant's Amendment dated May 22, 2003.

3. Applicant's arguments with respect to claims 1-33 under 35 U.S.C. 112, first paragraph, have been considered but are moot in view of the new ground(s) of rejection.

4. The rejection of claims 1, 3-17, 19, 21, 23, 25, 27, 29-31, and 33 under 35 U.S.C. 112, second paragraph, has been rendered moot in view of Applicant's Amendments/Arguments dated May 22, 2003.

5. The rejection of claims 1-11 under 35 U.S.C § 103(a), is maintained for the reasons of record set forth in the Office Action dated December 9, 2002. Applicant's

arguments in regards to claims 12-15 are convincing and have overcome the rejection under 35 U.S.C. 103(a).

6. The rejection of claim 17 under 35 U.S.C § 103(a) has been rendered moot in view of Applicant's Amendment dated May 22, 2003.

Objections/Rejections Set For the in Office Action dated December 9, 2002

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 16-17 are rejected under 35 U.S.C. 101 because the claimed recitation of a use or an intended, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods and compounds of formula (I) wherein R^3 is derived from fluorescein, does not reasonably provide enablement of compounds of formula (I) wherein R^3 is generically described as a label (other than labels derived from fluorescein), protein, enzyme, fatty acid, or peptide. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims without undue experimentation.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

The factors include, but are not limited to:

1. The breadth of the claims,
2. The nature of the invention,
3. The state of the prior art,
4. The level of one of ordinary skill,
5. The level of predictability in the art,
6. The amount of direction provided by the inventor,
7. The existence of working examples, and
8. The quantity of experimentation needed to make and/or use the invention based on the content of the disclosure.

Claims 1-11 are drawn to a process for manufacturing a 3'-labeled nucleic acid fragment comprising the enzymatic incorporation of a nucleotide derivative having as a precursor a compound of formula (I), at the 3' OH end of the nucleic acid fragment. The nucleotide derivative is further defined by the variable R^2 which is further defined by the variable R^3 wherein R^3 is a group derived from a label, a protein, an enzyme, a fatty acid, or a peptide. Claims 12-15 are drawn to a morpholino-nucleotide of formula (I).

Claim 16 is drawn to a process for manufacturing a morpholino-nucleotide of formula (I). Claim 17 is drawn to the use of a morpholino-nucleotide of formula (I).

The nature of the invention requires a close look at that which is provided in the claims and the scope of the content encompassed by the claim language. The instantly claimed invention relates to a process for manufacturing a 3'-labelled nucleic acid fragment comprising the enzymatic incorporation of a nucleotide derivative having as a precursor a compound of formula (I), at the 3' OH end of the nucleic acid fragment.

Morpholino oligonucleotide analogs and their preparation are well known in the art. Production may be carried out on automated synthesizes. The oligonucleotide analogs may also incorporate probes. Probes may be labeled by several methods typically used in the art. Typical probes include radioisotopes, fluorophores, chemiluminescent agents, and enzymes. The choice label dictates the manner in which the label is incorporated into the probe (US 5,849,482; column 12, lines 19-44). Although the art teaches enzymes broadly, the innumerable possibilities incorporated by such a broad term as "enzyme" requires further guidance from the specification as to the nature of the enzymes.

A person of ordinary skill in the art would be an organic chemist or biochemist having a PhD.

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to enable the use and making of a 3'-labelled nucleic acid fragment comprising the enzymatic incorporation of a nucleotide derivative having as a precursor a compound of

formula (I), at the 3' OH end of the nucleic acid fragment wherein R^3 is generically described as a label (other than labels derived from fluorescein), protein, enzyme, fatty acid, or peptide. The diverse nature of labels, proteins, enzymes, fatty acids, and peptides requires further guidance from the instant specification as to which moieties included in the vast group are incorporated into the instantly disclosed nucleic acid fragment.

The working examples in the instant specification are limited to the synthesis of 3'-labelled nucleic acid fragments of formula (I) wherein R^2 is $-CH_2$-COOH, $-(CH_2)_4$-NH_2, or $-(CH_2)_4NHR^3$ in which R^3 is a group derived from fluorescein; use of morpholino T glycine for the analysis of DNA sequence; testing morpholino A putrescine and morpholino A fluorescein in sequencing; use of morpholino A puterescine (MATPP) and morpholino A fluorescein (MATPPF) for the template-dependent 3' labeling of DNA fragments, test of enzymatic incorporation of these compounds by three polymerases and a reverse transcriptase. This guidance is not seen to be sufficient to teach the skilled artisan in this field how to make and use compounds of formula (I) wherein R^3 is generically described as a label (other than labels are derived from fluorescein), protein, enzyme, fatty acid, or peptide.

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the preparation and use of use compounds of formula (I) wherein R^3 is generically described as a label (other than labels are derived from fluorescein), protein, enzyme, fatty acid, or peptide. The lack of guidance provided by

the instant specification as to the nature R^3 would indeed necessitate undue experimentation.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1, 3-17, 19, 21, 23, 25, 27, 29-31, and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 1 and 3 incorporate the parenthetical phrase "(DNA or RNA)". It is unclear if the terms included within the parentheses are intended to incorporate limitations into the claim. All claims and depending claims incorporating said parenthetical phrase are indefinite in all occurrences. The parenthesis should be removed.

Claims 1, 3, 10, 12-17, and 30-31 incorporate the phrases "derived from", "fluorescein derivatives", "biotin derivatives", "rhodamine derivatives", and/or "group derived from fluorescein". Applicant has failed to particularly point out the identity of the compounds and the modifications to said compounds which distinctly set forth the structural core modifications or chemical moieties effectuating said derivatization. In the absence of distinct modifications or derivatizing moieties, the terms "derived" and "derivatives" are indefinite in all occurrences since the metes and bounds of said "derivatives" and "derived" components cannot be ascertained.

Claim 3 is drawn to a "process for sequencing a nucleic acid". It is unclear whether this process is drawn to synthesizing a nucleic a nucleic acid of a know sequence or drawn to a process for determining sequence of a nucleic acid which is unknown. The lack of clarity renders claim 5 and all subsequent depending claims indefinite.

In claims 4-5, 19, 21, and subsequent depending claims, it is unclear which "enzyme" is being referenced since claim 3, from which claims 4-5, 19, and 21 depend, recites "enzymatic polymerization" and "R^3 is a group derived from ...a enzyme".

Claim 16 is drawn to a process for manufacturing a morpholino-nucleotide; however, no active steps are set forth to practice said process. In the absence of any positive active procedural steps, the skilled artisan would not be apprised of the metes and bounds of the said process.

Claim 17 provides for the use of a morpholino-nucleotide of formula (I), but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims which depend from an indefinite claim are indefinite and are rejected for the reasons set forth herein above under 35 U.S.C. 122, second paragraph.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Torrence et al. U.S. Patent 4,515,781 (Torrence), Iversen U.S. Patent

6,365,577 B1 (priority from Provisional application 60/105,695 filed October 26, 1998) (Iversen), and Meyer, Jr. et al. U.S. Patent 5,849,482 (Meyer).

Claims 1-11 are drawn to a process for manufacturing a 3'-labeled nucleic acid fragment comprising the enzymatic incorporation of a nucleotide derivative having as a precursor a compound of formula (I), at the 3' OH end of the nucleic acid fragment. The nucleotide derivative is further defined by the variable R^2 which is further defined by the variable R^3 wherein R^3 is a group derived from a label, a protein, an enzyme, a fatty acid, or a peptide. Claim 3 is drawn to a "process for sequencing a nucleic acid". It is unclear whether this process is drawn to synthesizing a nucleic a nucleic acid of a know sequence or drawn to a process for determining sequence of a nucleic acid which is unknown. The examiner is interpreting the invention as being drawn to a process for synthesizing a nucleic a nucleic acid of a known sequence. Claims 12-15 are drawn to a morpholino-nucleotide of formula (I). Claim 16 is drawn to a process for manufacturing a morpholino-nucleotide of formula (I).

Torrence teaches a morpholino-nucleotide of formula (I) used for fine-tuning in antitumoral chemotherapy wherein m is 0-4, Y is H, n is 1-15, Z is H or a C_{1-50} hydrocarbon or substituted hydrocarbon bonded to the N of the morpholino ring through one of its carbon atoms (column 3, lines 1-36; column 4, lines 31-68; column 5).

Torrence differs from the instantly claimed invention in that the morpholino-nucleotide of formula (I) is described generically and Torrence does not teach a method of preparation. These deficiencies are, however, addressed by Iversen and Meyer.

Iversen teaches antisense agents comprising nucleotide subunits joined by internucleotide backbone linkages which present the nucleotide bases for hybridization with target RNA sequences (column 5, lines 16-20). Iversen teaches various oligonucleotide analogs modified at the backbone, the sugar moiety, or the bases themselves. Such analogs include, for example, morpholino oligonucleotides (column 5, lines 36-45). The preparation of the antisense agents is well know in the art, and may often be conveniently carried out on automated synthesizers. Iversen further teaches a general procedure for synthesis of S-OD, C-5-P, and uncharged morpholino antisense oligonucleotides (column 5, lines 48-52; Example 1). A summary of a typical synthesis is as follows: 1 μmol silica gel support column with the 3' base of the morpholino nucleotide analog linked by the 3'hydroxy group is inserted, and synthesis is carried out in a base by base fashion from the 3' to 5' direction (column 14, lines 17-22).

Meyer teaches oligonucleotides which have at least one cross-linking agent covalently attached to the oligonucleotide. The cross-linking function typically includes a linker arm and an electrophilic reactive group which, after complexing with the target sequence of DNA or mRNA is capable of reacting with the target DNA to form a covalent bond therewith (column 5, lines 16-25). The cross-linking agents may be attached to either the heterocyclic bases, to the sugars or modified sugars, or to the phosphate or modified phosphate moieties (column 5, lines 31-34). The preparation of modified sugars and of their respective "nucleosides" wherein such sugars or analogs are attached to a heterocyclic base (nucleic acid base) per se is known (column 6, lines 2-8). Meyer further teaches the utilization of the oligonucleotides as hybridization

probes and evidence of sequence specific cross-linking to single stranded DNA (column 12, lines 7-18). Probes may be labeled by several methods typically used in the art. Typical probes include radioisotopes, fluorophores, chemiluminescent agents, and enzymes. The choice label dictates the manner in which the label is incorporated into the probe (US 5,849,482; column 12, lines 19-44). The radioactive nucleotides can be incorporated into probes, for example, by using DNA synthesizers, by nick-translation, by tailing of radioactive bases in the 3' end of probes with terminal transferase, or by copying M13 plasmids having specific inserts with the Klenow fragment of DNA polymerase in the presence of radioactive dNTP's (column 12, lines 33-44).

It would have been obvious to one of ordinary skill in the art at the time of the invention combine the teachings of Torrence, Iversen, and Meyer to obtain the instantly claimed invention. The incorporation of a morpholino into a polymeric structure via 3' end is known in the art. The art teaches manufacture, modification via elongation, and sequencing using an automated synthesizer. The Klenow fragment and other enzymes known in the art are recognized as interchangeable. One would have been motivated to combine the teachings to produce pharmaceuticals useful for treating proliferative cell disorders.

17. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Torrence et al. U.S. Patent 4,515,781 (Torrence), Iversen U.S. Patent 6,365,577 B1 (priority from Provisional application 60/105,695 filed October 26, 1998) (Iversen), and Meyer, Jr. et al. U.S. Patent 5,849,482 (Meyer).

Claim 17 is drawn to the use of a morpholino-nucleotide of formula (I).

Torrence teaches a morpholino-nucleotide of formula (I) used for fine-tuning in antitumoral chemotherapy wherein m is 0-4, Y is H, n is 1-15, Z is H or a C_{1-50} hydrocarbon or substituted hydrocarbon bonded to the N of the morpholino ring through one of its carbon atoms (column 3, lines 1-36; column 4, lines 31-68; column 5).

Torrence differs from the instantly claimed invention in that the morpholino-nucleotide of formula (I) is described generically.

Iversen teaches antisense agents comprising nucleotide subunits joined by internucleotide backbone linkages which present the nucleotide bases for hybridization with target RNA sequences (column 5, lines 16-20). Iversen teaches various oligonucleotide analogs modified at the backbone, the sugar moiety, or the bases themselves. Such analogs include, for example, morpholino oligonucleotides (column 5, lines 36-45). The preparation of the antisense agents is well know in the art, and may often be conveniently carried out on automated synthesizers. Iversen further teaches a general procedure for synthesis of S-OD, C-5-P, and uncharged morpholino antisense oligonucleotides (column 5, lines 48-52; Example 1). A summary of a typical synthesis is as follows: 1 mol silica gel support column with the 3' base of the morpholino nucleotide analog linked by the 3'hydroxy group is inserted, and synthesis is carried out in a base by base fashion from the 3' to 5' direction (column 14, lines 17-22).

Meyer teaches oligonucleotides which have at least one cross-linking agent covalently attached to the oligonucleotide. The cross-linking function typically includes a linker arm and an electrophilic reactive group which, after complexing with the target sequence of DNA or mRNA is capable of reacting with the target DNA to form a

covalent bond therewith (column 5, lines 16-25). The cross-linking agents may be attached to either the heterocyclic bases, to the sugars or modified sugars, or to the phosphate or modified phosphate moieties (column 5, lines 31-34). The preparation of modified sugars and of their respective "nucleosides" wherein such sugars or analogs are attached to a heterocyclic base (nucleic acid base) per se is known (column 6, lines 2-8). Meyer further teaches the utilization of the oligonucleotides as hybridization probes and evidence of sequence specific cross-linking to single stranded DNA (column 12, lines 7-18). Probes may be labeled by several methods typically used in the art. Typical probes include radioisotopes, fluorophores, chemiluminescent agents, and enzymes. The choice label dictates the manner in which the label is incorporated into enzymes. The choice label dictates the manner in which the label is incorporated into the probe (US 5,849,482; column 12, lines 19-44). The radioactive nucleotides can be incorporated into probes, for example, by using DNA synthesizers, by nick-translation, by tailing of radioactive bases in the 3' end of probes with terminal transferase, or by copying M13 plasmids having specific inserts with the Klenow fragment of DNA polymerase in the presence of radioactive dNTP's (column 12, lines 33-44).

It would have been obvious to one of ordinary skill in the art at the time of the invention combine the teachings of Torrence, Iversen, and Meyer to obtain the instantly claimed invention. The incorporation of a morpholino into a polymeric structure via 3' end is known in the art. The art teaches manufacture, modification via elongation, and sequencing using an automated synthesizer. One would have been motivated to

combine the teachings to produce pharmaceuticals useful for treating proliferative cell disorders.

Response to Arguments

18. Applicant's arguments regarding the rejection of claims 1-16 under 35 U.S.C. 103(a) filed May 22, 2003 have been fully considered but they are not persuasive.

Applicant argues: 1) the art of record does not teach the morpholino-nucleotide of formula (I) nor its use in the instantly claimed process and 2) the skilled artisan would not have a reasonable expectation of success of attaining the instant invention based on the prior art. In response to applicant's assertion that the examiner has failed to establish a *prima facie* case of obviousness, the examiner respectfully disagrees.

Iversen teaches various oligonucleotide analogs modified at the backbone, the sugar moiety, or the bases themselves. Such analogs include, for example, morpholino oligonucleotides (column 5, lines 36-45). The preparation of the antisense agents is well know in the art, and may often be conveniently carried out on automated synthesizers. Iversen further teaches a general procedure for synthesis of S-OD, C-5-P, and uncharged morpholino antisense oligonucleotides (column 5, lines 48-52; Example 1). A summary of a typical synthesis is as follows: 1 μmol silica gel support column with the 3' base of the morpholino nucleotide analog linked by the 3'hydroxy group is inserted, and synthesis is carried out in a base by base fashion from the 3' to 5' direction (column 14, lines 17-22). Neither Iversen, Meyer, nor Torrence explicitly teaches the instantly claimed compounds of formula (I) in the instantly claimed process

claims. However, a long line of cases have held that the mere use of different starting materials, whether novel or known, in a conventional process to produce the product one would expect therefrom does not render the process unobvious. *In re Surrey et al.* (CCPA 1963) 319 F2d 233, 138 USPQ 67; *In re Kanter* (CCPA 1968) 399 F2d 249, 158 USPQ 331; *In re Larsen* (CCPA 1961) 292 F2d 531, 130 USPQ 209; *Ex parte Ryland et al.* (POBA 1948) 108 USPQ 15. The mere use of different starting materials, whether novel or known, in a conventional process to produce the product one would expect therefrom does not render the process unobvious. Thus, a process which, from the results obtained, is analogous to a prior art process is not patentable merely because the product thereof is novel and patentable, *Clinical Products, Ltd. V. Brenner, Comr. Pats.* (DCDC 1966) 255 FSupp 155, 149 USPQ 475, or because the applicant discloses a new benefit in addition to those which would be expected to be obtained. Once the general reaction has been shown to be old, the burden is on the applicant to present reason or authority for believing that a group on the starting compound would take part in or affect the basic reaction and thus alter the nature of the product or the operability of the process and thus the unobviousness of the method of producing it, *In re Neugebauer et al* (CCPA 1964) 330 F2d 353, 141 USPQ 205.

Regarding the assertion that there is no reasonable expectation of success and all of the claim limitations have not been taught, the examiner respectfully disagrees. It is indeed prima facie obvious to use of different starting materials, whether novel or known, in a conventional process to produce the product one would expect therefrom.

In the absence of some proof of a secondary nature to obviate the rejection as set forth in the Office Action dated December 9, 2002, or of some specific limitations which would tip the scale of patentability in the favor of the instantly claimed invention, it would have been obvious to one of ordinary skill in this art at the time of the invention to use the morpholino nucleotide of formula (I) in a process for manufacturing a nucleic acid fragment, a process for modifying a nucleic acid fragment, or method for sequencing a nucleic acid.

Information Disclosure Statement

19. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

20. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

21. Claims 1-11, 16, and 18-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which it pertains to make and use the invention as of its filing date, *In re Glass*, 181 USPQ 31; 492 F2.d 1228 (CCPA 1974).

A written description analysis involves three principle factors:

1. Field of the invention and predictability of the art
2. Breadth of the claims
3. For each claimed species/genus, possession of claimed invention at the time of the filing.

The instant specification is drawn to a process for manufacturing, modifying, or sequencing a 3'-labeled nucleic acid fragment comprising the enzymatic incorporation of a nucleotide derivative having as a precursor a compound of formula (I), at the 3' OH end of the nucleic acid fragment. The nucleotide derivative is further defined by the variable R^2 which is further defined by the variable R^3 wherein R^3 is a group derived from a label, a protein, an enzyme, a fatty acid, or a peptide.

Each of the terms "label", "protein", "enzyme", "fatty acid", "peptide", "photo-crosslinking agents", "antibodies", "hydrophobic peptides", "fluorophores", "radio active products", "luminescent products", "electorluminescent and fluorescent products", "molecules capable of coupling with other molecules", "molecules which allow interactions of the antigen-antibody type", "enzymatic labels", "heat-resistant polymerase of a Thermophilus bacterium", "terminal transferase", "reverse

transcriptase", and "derivatives" lack support wherein applicants fail to provide a written description which teaches how to make and use same in the instant process for preparing nucleotides or where applicants fail to teach how to use same incorporated into a nucleic acid fragment. The essential novelty, the essence of the invention, must be describe in such details, including proportions and techniques where necessary, as to enable those persons skilled in the art to make and utilize the invention. A broad claim requires a correlatively broad and sufficient disclosure to support it. Applicants do not provide an adequate written description which provides guidance for the preparation of nucleotide compounds within the scope of the invention. Applicants do not provide an adequate written description which provides guidance for the use of nucleotide compounds within the scope of the invention. Examples and description should be of sufficient scope as to justify the scope of the claims. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula. A disclosure involving a new chemical compound or composition must teach persons skilled in the art how to make the compound. The process is considered to be incomplete wherein applicants set forth the preparation of compounds wherein various moieties are left undefined in full, clear and exact terms (e.g. all moieties "derivatized" wherein the identity of the substituents intended to effectuate said derivatization are not set forth in any synthetic procedural steps or any specific compound containing same is utilized in any specific method).

22. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

23. Claims 8, 16, 22-23, and 26-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 26-27 recite the phrases "molecules capable of coupling with other molecules" and/or "molecules which allow interactions of the antigen-antibody type". Said phrases do not convey a structural formula or chemical name to one of ordinary skill in the art. In the absence of a structural formula or chemical name, all claims reading upon said phrases are indefinite as one of ordinary skill in the art is not apprised of the metes and bounds of the claimed invention.

Claim 16 recites the phrases "R^1 has the meaning given above" and "R^2 has the meaning given above". In all occurrences, phrases referencing the meaning of a variable as defined in some alternative, preceding location, such as "above", without distinct reference to the particular location of said meaning or definition, renders the claim(s) in which said phrase(s) appear indefinite. The reference to some alternative location for a definition is superfluous if the definition or meaning is already set forth in a claim or said definition or meaning is clearly set forth in an independent claim from which a claim depends. In all occurrences and under these circumstances, the phrases should be deleted from the claims as superfluous.

Claims 22-23 recite the term "derivatives thereof". In the absence of distinct modifications to the chemical core claimed or distinct language to describe the structural modifications or the chemical names of modified compounds of this invention, the

identity of said modified compounds would be difficult to describe and the metes and bounds of said modified compounds applicant regards as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claims.

Claim Rejections - 35 USC § 103

24. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

25. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

26. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

27. Claims 1-11, 16, and 18-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Torrence et al. U.S. Patent 4,515,781 (Torrence), Iversen U.S. Patent 6,365,577 B1 (priority from Provisional application 60/105,695 filed October 26, 1998) (Iversen), and Meyer, Jr. et al. U.S. Patent 5,849,482 (Meyer).

Claims 1-11, 16, and 18-33 are drawn to a process for manufacturing, modifying, or sequencing a 3'-labeled nucleic acid fragment comprising the enzymatic incorporation of a nucleotide derivative having as a precursor a compound of formula (I), at the 3' OH end of the nucleic acid fragment.

Torrence teaches a morpholino-nucleotide of formula (I) used for fine-tuning in antitumoral chemotherapy wherein m is 0-4, Y is H, n is 1-15, Z is H or a C_{1-50} hydrocarbon or substituted hydrocarbon bonded to the N of the morpholino ring through one of its carbon atoms (column 3, lines 1-36; column 4, lines 31-68; column 5).

Torrence differs from the instantly claimed invention in that the morpholino-nucleotide of formula (I) is described generically and Torrence does not teach a method of preparation. These deficiencies are, however, addressed by Iversen and Meyer.

Iversen teaches antisense agents comprising nucleotide subunits joined by internucleotide backbone linkages which present the nucleotide bases for hybridization with target RNA sequences (column 5, lines 16-20). Iversen teaches various oligonucleotide analogs modified at the backbone, the sugar moiety, or the bases themselves. Such analogs include, for example, morpholino oligonucleotides (column 5, lines 36-45). The preparation of the antisense agents is well know in the art, and may often be conveniently carried out on automated synthesizers. Iversen further

teaches a general procedure for synthesis of S-OD, C-5-P, and uncharged morpholino antisense oligonucleotides (column 5, lines 48-52; Example 1). A summary of a typical synthesis is as follows: 1 μmol silica gel support column with the 3' base of the morpholino nucleotide analog linked by the 3'hydroxy group is inserted, and synthesis is carried out in a base by base fashion from the 3' to 5' direction (column 14, lines 17-22).

Meyer teaches oligonucleotides which have at least one cross-linking agent covalently attached to the oligonucleotide. The cross-linking function typically includes a linker arm and an electrophilic reactive group which, after complexing with the target sequence of DNA or mRNA is capable of reacting with the target DNA to form a covalent bond therewith (column 5, lines 16-25). The cross-linking agents may be attached to either the heterocyclic bases, to the sugars or modified sugars, or to the phosphate or modified phosphate moieties (column 5, lines 31-34). The preparation of modified sugars and of their respective "nucleosides" wherein such sugars or analogs are attached to a heterocyclic base (nucleic acid base) per se is known (column 6, lines 2-8). Meyer further teaches the utilization of the oligonucleotides as hybridization probes and evidence of sequence specific cross-linking to single stranded DNA (column 12, lines 7-18). Probes may be labeled by several methods typically used in the art. Typical probes include radioisotopes, fluorophores, chemiluminescent agents, and enzymes. The choice label dictates the manner in which the label is incorporated into the probe (US 5,849,482; column 12, lines 19-44). The radioactive nucleotides can be incorporated into probes, for example, by using DNA synthesizers, by nick-translation, by tailing of radioactive bases in the 3' end of probes with terminal transferase, or by

copying M13 plasmids having specific inserts with the Klenow fragment of DNA polymerase in the presence of radioactive dNTP's (column 12, lines 33-44).

It would have been obvious to one of ordinary skill in the art at the time of the invention combine the teachings of Torrence, Iversen, and Meyer to obtain the instantly claimed invention. The incorporation of a morpholino into a polymeric structure via 3' end is known in the art. The art teaches manufacture, modification via elongation, and sequencing using an automated synthesizer. The Klenow fragment and other enzymes known in the art are recognized as interchangeable. One would have been motivated to combine the teachings to produce pharmaceuticals useful for treating proliferative cell disorders.

1. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Torrence et al. U.S. Patent 4,515,781 (Torrence), Iversen U.S. Patent 6,365,577 B1 (priority from Provisional application 60/105,695 filed October 26, 1998) (Iversen), and Meyer, Jr. et al. U.S. Patent 5,849,482 (Meyer).

Claim 17 is drawn to the use of a morpholino-nucleotide of formula (I).

Torrence teaches a morpholino-nucleotide of formula (I) used for fine-tuning in antitumoral chemotherapy wherein m is 0-4, Y is H, n is 1-15, Z is H or a C_{1-50} hydrocarbon or substituted hydrocarbon bonded to the N of the morpholino ring through one of its carbon atoms (column 3, lines 1-36; column 4, lines 31-68; column 5).

Torrence differs from the instantly claimed invention in that the morpholino-nucleotide of formula (I) is described generically.

Iversen teaches antisense agents comprising nucleotide subunits joined by internucleotide backbone linkages which present the nucleotide bases for hybridization with target RNA sequences (column 5, lines 16-20). Iversen teaches various oligonucleotide analogs modified at the backbone, the sugar moiety, or the bases themselves. Such analogs include, for example, morpholino oligonucleotides (column 5, lines 36-45). The preparation of the antisense agents is well know in the art, and may often be conveniently carried out on automated synthesizers. Iversen further teaches a general procedure for synthesis of S-OD, C-5-P, and uncharged morpholino antisense oligonucleotides (column 5, lines 48-52; Example 1). A summary of a typical synthesis is as follows: 1 μmol silica gel support column with the 3' base of the morpholino nucleotide analog linked by the 3'hydroxy group is inserted, and synthesis is carried out in a base by base fashion from the 3' to 5' direction (column 14, lines 17-22).

Meyer teaches oligonucleotides which have at least one cross-linking agent covalently attached to the oligonucleotide. The cross-linking function typically includes a linker arm and an electrophilic reactive group which, after complexing with the target sequence of DNA or mRNA is capable of reacting with the target DNA to form a covalent bond therewith (column 5, lines 16-25). The cross-linking agents may be attached to either the heterocyclic bases, to the sugars or modified sugars, or to the phosphate or modified phosphate moieties (column 5, lines 31-34). The preparation of modified sugars and of their respective "nucleosides" wherein such sugars or analogs are attached to a heterocyclic base (nucleic acid base) per se is known (column 6, lines 2-8). Meyer further teaches the utilization of the oligonucleotides as hybridization

probes and evidence of sequence specific cross-linking to single stranded DNA (column 12, lines 7-18). Probes may be labeled by several methods typically used in the art. Typical probes include radioisotopes, fluorophores, chemiluminescent agents, and enzymes. The choice label dictates the manner in which the label is incorporated into enzymes. The choice label dictates the manner in which the label is incorporated into the probe (US 5,849,482; column 12, lines 19-44). The radioactive nucleotides can be incorporated into probes, for example, by using DNA synthesizers, by nick-translation, by tailing of radioactive bases in the 3' end of probes with terminal transferase, or by copying M13 plasmids having specific inserts with the Klenow fragment of DNA polymerase in the presence of radioactive dNTP's (column 12, lines 33-44).

It would have been obvious to one of ordinary skill in the art at the time of the invention combine the teachings of Torrence, Iversen, and Meyer to obtain the instantly claimed invention. The incorporation of a morpholino into a polymeric structure via 3' end is known in the art. The art teaches manufacture, modification via elongation, and sequencing using an automated synthesizer. One would have been motivated to combine the teachings to produce pharmaceuticals useful for treating proliferative cell disorders.

Conclusion

28. Claims 1-16 and 18-33 are pending. Claims 1-11, 16, and 18-33 are rejected. Claims 12-15 appear to be free of the prior art.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 703-305-4043. The examiner can normally be reached on M-F 8:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Patrick T. Lewis, PhD
Examiner
Art Unit 1623

James O. Wilson
Supervisory Patent Examiner
Technology Center 1600

ptl
August 8, 2003